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1,6-Dihydro-3(2H)-pyridinones. X.[1] 2-Azabicyclo[2.2.2]octane Ring Formation *via* Intramolecular Michael Reaction: Total Synthesis of (±)-Ibogamine and (±)-Epiibogamine[2]

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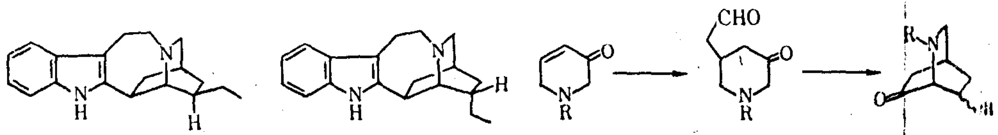
A new elaboration method for the 2-azabicyclo[2.2.2]octane ring *via* an intramolecular Michael reaction has been developed and applied to the total synthesis of (±)-ibogamine (**1**) and (±)-epiibogamine (**2**). The unsaturated ester (**9**) derived from ethyl 1,6-dihydro-3(2H)-pyridinone-1-carboxylate (**3a**) was reacted with potassium carbonate or sodium hydride to provide two 2-azabicyclo[2.2.2]octanone derivatives (**19** and **20**), the stereochemistry of which was confirmed by chemical evidence. By a three-step sequence, the esters (**19** and **20**) were converted into **27** and **36**, which were then transformed into the corresponding amides (**31** and **40**). Cyclization of **31** and **40** followed by reduction with a complex of lithium aluminum hydride–aluminum chloride furnished (±)-epiibogamine (**2**) and (±)-ibogamine (**1**), respectively, in good yields.

Keywords——dihydropyridinone; synthon; intramolecular Michael reaction; indole alkaloid; ibogamine; epiibogamine; total synthesis

Ibogamine (**1**), a representative alkaloid of the Iboga alkaloids, has been the target of a number of synthetic investigations because it possesses a unique framework, the 2-azabicyclo[2.2.2]octane ring, in its molecule.[3] Since Büchi and his co-workers reported the first total synthesis of (±)-ibogamine (**1**) and (±)-epiibogamine (**2**) in 1965,[4] several successful syntheses of **1** and/or **2** have been reported.[5] In each of these syntheses the elaboration of a 2-azabicyclo[2.2.2]octane derivative bearing a two-carbon chain at the requisite position of the ring had been the crucial step.

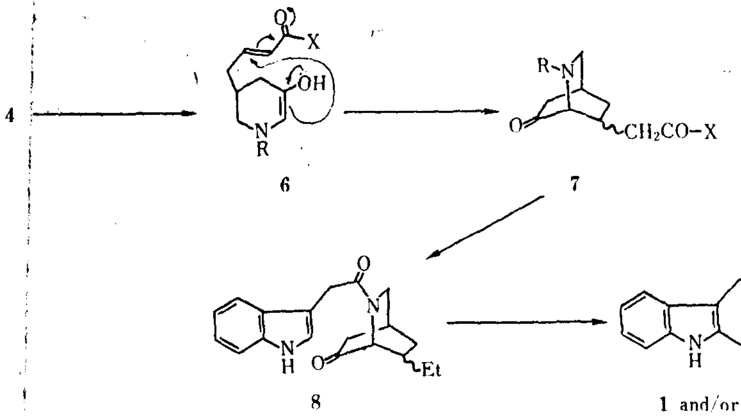
In the preceding papers of this series, we reported a novel synthesis of N-substituted 1,6-dihydro-3(2H)-pyridinones (**3**)[6] and found that the keto aldehyde (**4**) derived from **3** readily afforded the 2-azabicyclo[2.2.2]octanones (**5**) through an intramolecular aldol reaction.[7] As an application to alkaloid syntheses, we wish to present here a new elaboration method for a 2-azabicyclo[2.2.2]octane compound bearing a two-carbon chain, and its application to a total synthesis of (±)-ibogamine (**1**) and (±)-epiibogamine (**2**).



1 2 3a : R=CO$_2$Et 4 5
3b : R=Cbz
3c : R=SO$_2$Me

Chart 1

The present strategy for synthesis of the Iboga alkaloids involves an intramolecular Michael addition reaction as the key step to construct the 2-azabicyclo[2.2.2]octane ring. In view of the previous result that the keto aldehyde (**4**) smoothly cyclized to **5**, the vinylogous derivative (**6**) of **4** should serve as a potential intermediate to the desired compound (**7**), which should be convertible into the amide (**8**) by chemical modifications of the C-7 substituent and *N*-protecting group. For preparation of **6** from **4** or its equivalent, the Horner–Emmons reaction seems to be a suitable tool. The last step should be easily achievable by the known procedure[5b)] or its modification.



6 7 8 1 and/or 2

Chart 2

Construction of the 2-Azabicyclo[2.2.2]octane Ring by an Intramolecular Michael Reaction

When the substituent X in **6** is hydrogen, some side reactions proceed in competition with the desired reaction.[8)] In order to avoid such complexity we choose the alkoxyl group as the substituent X. Benzyl (*E*)-5-(3-ethoxycarbonyl-2-propenyl)-3-oxopiperidine-1-carboxylate (**9**), the starting material to be subjected to the intramolecular Michael reaction, was prepared by two alternative sequences as shown in Chart 3. The acetal (**10**)[7)] which was previously obtained from **3a** was treated with 1% hydrochloric acid in acetone to give the aldehyde (**11**) in 68% yield along with the starting material (**10**; 12% yield).[9)] The Horner–Emmons reaction of **11** with the ylid of triethyl phosphonoacetate[10)] in benzene provided the (*E*)-olefin (**13**) as a sole product in 97% yield, and this was hydrolyzed with 6 N hydrochloric acid to give the desired ketone (**9**) in 59% yield.[11)] In order to improve the yield of **9**, the second method was examined next. Ethyl 5-(2-ethylenedioxyethyl)-3-hydroxypiperidine-1-carboxylate (**14**),[7)] a precursor of **10**, was subjected to basic hydrolysis to afford the amine (**15**), exposure of which to carbobenzoxy chloride in a usual manner yielded the benzyl urethane (**16**) in 90% yield from **14**. On acidic hydrolysis, the acetal (**16**) provided the aldehyde (**17**), the Horner–Emmons reaction of which was followed by oxidation with the Jones reagent[12)] to give **9** more effectively.[13)]

Although all efforts to achieve the intramolecular cyclization of **9** in acidic media[14)] resulted in either complete recovery of the starting material or only the formation of undefined complex mixtures, basic conditions were found to be suitable for this purpose. Namely, on treatment with potassium carbonate in refluxing ethanol, **9** provided two diastereoisomeric 2-azabicyclo[2.2.2]octanones (**19** and **20**) in 73 and 15% yields, respectively. On the other hand, when the reaction was carried out with sodium hydride in dioxane, the yields of **19** and **20** changed to 51 and 26%, respectively. Since each isomer did not isomerize into the other under the conditions employed above, these results seem to reflect a kinetically controlled reaction under these conditions. The predominant formation of **19** can be well interpreted in terms of non-bonded interaction. Namely, the transition state (9B) for **20** is anticipated to be more unstable than the other one (9A) because of a severe steric repulsion

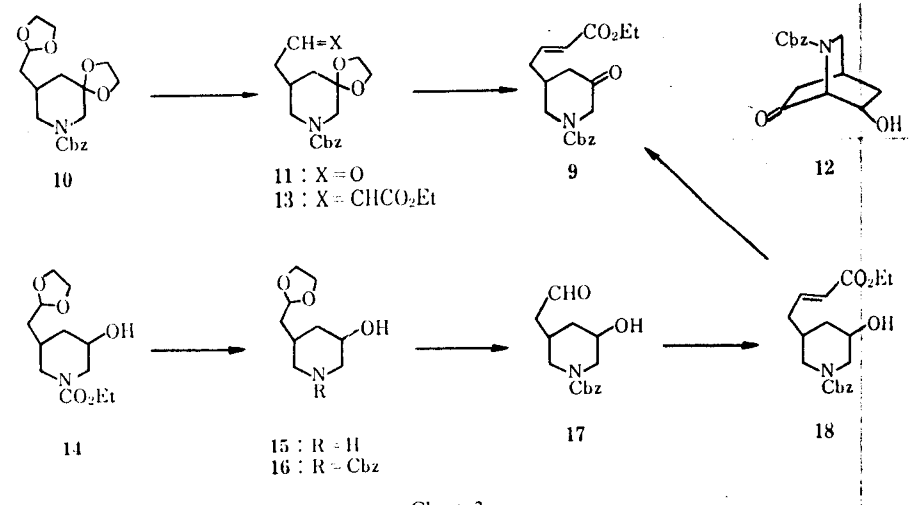


Chart 3

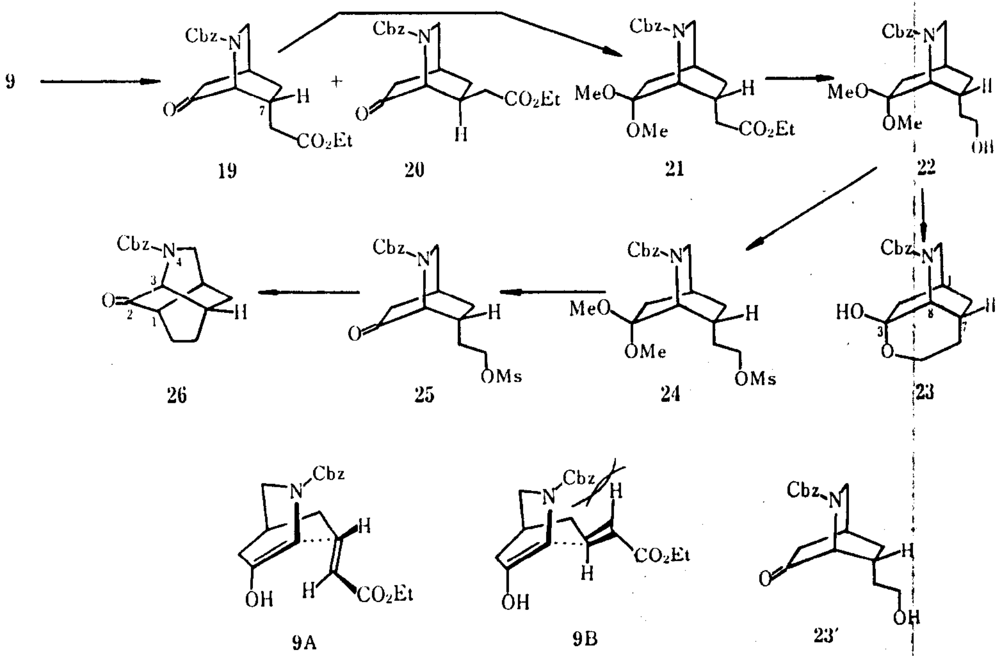


Chart 4

between the *N*-substituent and the olefin part as depicted in Chart 4.

The stereochemistry of the products (**19** and **20**) was completely confirmed by the following chemical evidence. The major product (**19**) was converted into the ketal (**21**) in a usual manner and a chemoselective reduction of the ester part in **21** was accomplished by careful reduction with lithium aluminum hydride in ether to result in exclusive formation of the alcohol (**22**) in 92% overall yield. On treatment with 1% hydrochloric acid in acetone, **22** provided the hemi-acetal (**23**), mp 85—87 °C, in 83% yield. The infrared (IR) spectrum of **23** showed no ketonic band in the crystalline state, while it showed a weak ketonic absorption at 1735 cm^{-1} in chloroform solution, indicating that the hemi-acetal (**23**) exists in equilibrium with the ketol (23′) in solution. On the other hand, the mesylate (24) which was obtained from 22 in a usual manner in 96% yield was hydrolyzed to the ketone (25). Exposure of 25 to sodium hydride in dry *N*,*N*-dimethylformamide (DMF) at room temperature[15] afforded an azatwistanone derivative (26), though in a low yield. Now, it is clear that the major product (19) possesses the *endo* orientation of the C-7 substituent because of its conversion into 23 and 26.

Total Synthesis of (±)-Epiibogamine (2)

Epiibogamine (2) is an Iboga alkaloid isolated from *Melodinus aeneus* in 1978.[16] The major product (19) obtained by the intramolecular Michael reaction of 9 was used for the synthesis of (±)-epiibogamine (2). The mesylate (24) was reduced with zinc and sodium iodide[17] in boiling 1,2-dimethoxyethane (DME), providing the reduced product (27) in 85% yield. Although attempts to remove the *N*-substituent in 27 by hydrogenation over 5% palladium on carbon were unsuccessful, the ketone (28), the hydrolyzed product of 27, smoothly underwent hydrogenolysis to give the labile amine (29). Without purification, 29 was acylated with 3-indolylacetyl chloride[18] to afford the amide (30) in overall 93% yield from 27. Ketalization of 30 with methyl orthoformate to 31 followed by treatment with *p*-toluenesulfonic acid in boiling benzene for a short time gave the pentacyclic product (32) in 64% yield.

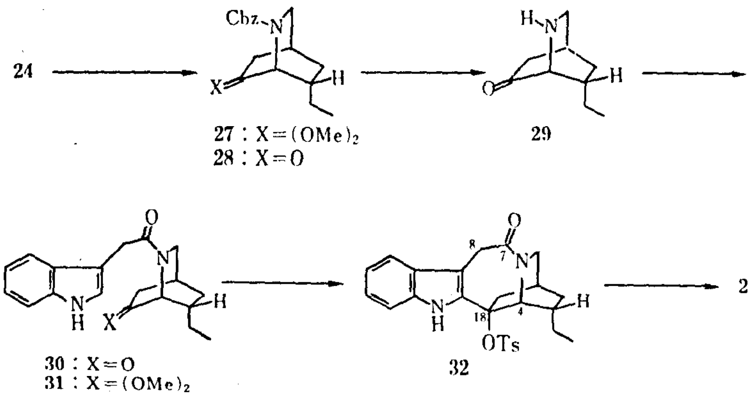


Chart 5

Nagata *et al.* have already described the conversion of 32 into (±)-epiibogamine (2) by a five-step sequence,[19] but the total yield was very low. In order to improve the sequence, we have investigated a one-step route to (±)-epiibogamine (2) from 32. After some unsuccessful attempts, a reduction method using a mixture of lithium aluminum hydride and aluminum chloride was found to be suitable for the present purpose. Treatment of 32 with a 1 : 1 mixture of the reagents[20] in tetrahydrofuran (THF) at room temperature resulted in the exclusive formation of (±)-epiibogamine (2) in 86% yield.

Total Synthesis of (±)-Ibogamine (1)

In the same manner as described for (±)-epiibogamine (2), (±)-ibogamine (1) was synthesized from the minor product (20) of the intramolecular Michael reaction of 9. Ketalization of 20 to 33 was followed by reduction with lithium aluminum hydride to afford the alcohol (34) in 86% yield. Reductive removal of the hydroxyl group in 34 *via* the mesylate (35) yielded 36 (77% yield from 34), which was hydrolyzed, hydrogenolyzed, and then acylated to give the amide (39) in 81% yield. The dimethyl ketal (40), obtained from 39 in 99% yield, was cyclized to the tosylate (41), which was finally transformed into (±)-ibogamine (1)

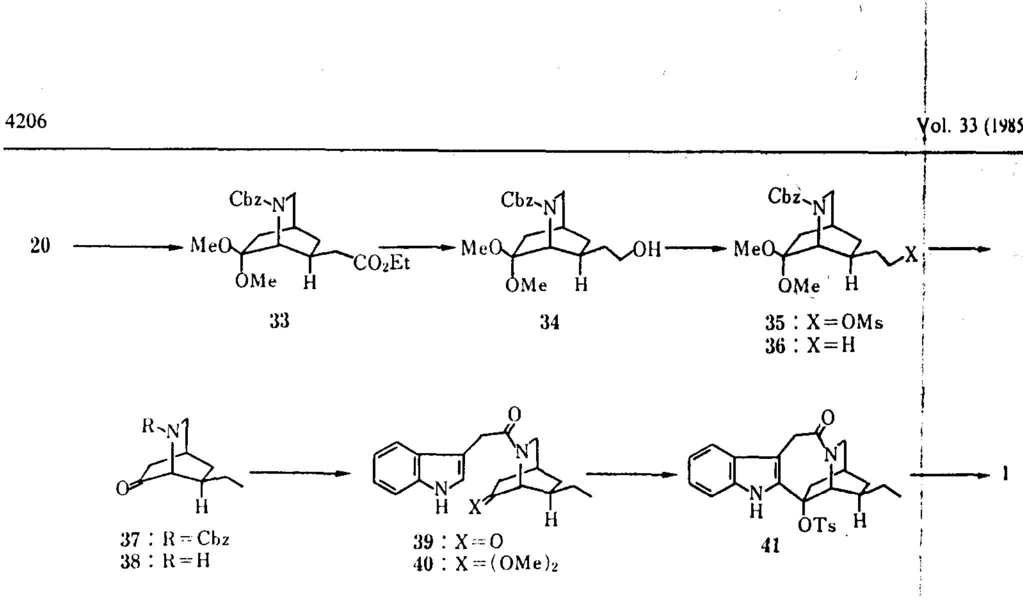


Chart 6

in 53% yield from **40**.

The synthesized (±)-ibogamine and (±)-epiibogamine were proved to be identical with the corresponding natural products by means of spectral comparisons. The present synthesis of **1** and **2** requires 16 steps from the hydroxy acetal (**14**) and seems to be of great value from the viewpoint of its potential applicability to the synthesis of some oxygenated Iboga alkaloids,[21] *e.g.* albifloranine, heyneanine, and isovoacristine.

Experimental

All melting points are uncorrected. IR spectra were measured with a JASCO A-102 spectrometer. Mass spectra (MS) were obtained with a Hitachi M-80 mass spectrometer at 75 eV. Unless otherwise noted, proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined in $CDCl_3$ solutions at 25 °C on a JEOL PMX-60 or JEOL FX-100 spectrometer using Me_4Si as an internal standard. Organic extracts were dried over anhydrous Na_2SO_4 and the solvents were removed in a rotary evaporator under reduced pressure. Column chromatography was carried out with Silica gel 60 (Merck) or Alumina 90 (Merck).

Benzyl 9-(2-Oxoethyl)-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (11)——A solution of benzyl 9-(2-ethylenedioxyethyl)-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (**10**; 1.23 g)[7] in acetone (20 ml) containing 1% HCl (6 ml) was refluxed with stirring for 1 h. The organic solvent was evaporated off at room temperature and the residue was extracted with $CHCl_3$ (20 ml × 3). The extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on alumina. The first fraction eluted with $CHCl_3$–C_6H_6 afforded 193 mg (16%) of the starting material (**10**) and the second one afforded 732 mg (68%) of **11** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2720 (CHO), 1720 (CO), 1685 (NCOO). ^{1}H-NMR δ: 3.88 (4H, s, OCH_2CH_2O), 5.08 (2H, s, CH_2Ar), 7.26 (5H, s, Ar-H), 9.60 (1H, br s, CHO). MS *m/e* (%): 319 (0.8, M$^+$), 141 (100).

Benzyl (*E*)-9-(3-Ethoxycarbonyl-2-propenyl)-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (13)——A solution of triethyl phosphonoacetate (617 mg) in dry C_6H_6 (5 ml) was added dropwise to a stirred suspension of NaH (50%, in oil; 66 mg) in dry C_6H_6 (10 ml) under ice cooling over a period of 10 min, and stirring was continued for another 30 min at room temperature. A solution of **11** (732 mg) in dry C_6H_6 (5 ml) was added to the resulting solution under ice cooling over a period of 1 min and stirring was further continued for 1 h at room temperature. Water (10 ml) and C_6H_6 (30 ml) were added to the mixture and the organic layer was separated. The organic layer was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on alumina in $CHCl_3$ to afford 862 mg (97%) of **13** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685 br (COO, NCOO), 1650 (C=C). ^{1}H-NMR δ: 1.27 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.88 (4H, s, OCH_2CH_2O), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.08 (2H, s, CH_2Ar), 5.72 (1H, d, J=16 Hz, $CH=C\underline{H}CO$), 6.5—7.0 (1H, m, $C\underline{H}=CHCO$), 7.25 (5H, s, Ar-H). MS *m/e* (%): 389 (35, M$^+$), 211 (100).

Benzyl 5-(2-Ethylenedioxyethyl)-3-hydroxypiperidine-1-carboxylate (16)——A solution of KOH (1.2 g) in water (15 ml) was added to a solution of ethyl 5-(2-ethylenedioxyethyl)-3-hydroxypiperidine-1-carboxylate (**14**; 1.08 g)[7] in ethanol (15 ml), and the mixture was refluxed with stirring for 93 h. The ethanol was evaporated off and the residue was diluted with water (60 ml). The resulting aqueous solution was washed with ether (20 ml) in order to remove neutral impurities. Carbobenzoxy chloride (0.70 ml) and $CHCl_3$ (30 ml) was added to the aqueous solution and the whole was stirred under ice cooling for 1 h. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (30 ml). The combined organic layer was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (20 : 1) to afford 1.21 g (90%) of **16** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1680 (NCOO). ^{1}H-NMR δ: 4.83 (1H, t, $J=4.5$ Hz, $CH\langle^{O}_{O}$), 5.05 (2H, s, CH_2Ar), 7.23 (5H, s, Ar-H). The product was proved to be identical with an authentic sample[22] of **16** by means of thin-layer chromatography (TLC), IR, and ^{1}H-NMR comparisons.

Benzyl 3-Hydroxy-5-(2-oxoethyl)piperidine-1-carboxylate (17)——A solution of **16** (804 mg) in purified acetone (18 ml) containing 1% HCl (9 ml) was refluxed with stirring for 1.5 h. Work-up as usual gave 681 mg (98%) of crude **17** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 2720 (CHO), 1720 (CO), 1680 (NCOO). ^{1}H-NMR δ: 2.37 (2H, dd, $J=4$, 1 Hz, $C\underline{H}_2CHO$), 5.07 (2H, s, CH_2Ar), 7.25 (5H, s, Ar-H), 9.58 (1H, t, $J=1$ Hz, CHO). MS *m/e* (%): 277 (0.75, M^+), 91 (100). High-resolution MS Calcd for $C_{15}H_{19}NO_4$: 277.1313. Found: 277.1321.

Benzyl (*E*)-5-(3-Ethoxycarbonyl-2-propenyl)-3-hydroxypiperidine-1-carboxylate (18)——A solution of triethyl phosphonoacetate (561 mg) in dry C_6H_6 (5 ml) was added dropwise to a stirred suspension of NaH (50% in oil; 60 mg) in dry C_6H_6 (10 ml) under ice cooling over a period of 10 min, and stirring was continued for another 30 min at room temperature. To the resulting solution, a solution of **17** (681 mg) in dry C_6H_6 (10 ml) was added under ice cooling over a period of 3 min, and stirring was continued for another 5 min under cooling. Work-up as usual gave an oily residue, which was chromatographed on alumina in $CHCl_3$–C_6H_6 (2 : 1) to afford 740 mg (85% from **16**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1680 (COO, NCOO), 1650 sh (C=C). ^{1}H-NMR δ: 1.25 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 4.23 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 5.07 (2H, s, CH_2Ar), 5.77 (1H, d, $J=15$ Hz, $CH=C\underline{H}CO$), 6.6—7.0 (1H, m, $C\underline{H}=CHCO$), 7.24 (5H, s, Ar-H). MS *m/e* (%): 347 (7.8, M^+), 212 (100). High-resolution MS Calcd for $C_{19}H_{25}NO_5$: 347.1731. Found: 347.1716.

Benzyl (*E*)-5-(3-Ethoxycarbonyl-2-propenyl)-3-oxopiperidine-1-carboxylate (9)——a) From **13**: A mixture of **13** (860 mg), 6 N HCl (6 ml), and purified acetone (12 ml) was refluxed for 50 min. The organic solvent was evaporated off and the residue was extracted with $CHCl_3$ (20 ml × 3). The extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on alumina in $CHCl_3$ to afford 451 mg (59%) of **9** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (COO), 1695 (NCOO), 1650 (C=C). ^{1}H-NMR δ: 1.27 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 4.13 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 5.10 (2H, s, CH_2Ar), 5.80 (1H, d, $J=16$ Hz, $CH=C\underline{H}CO$), 6.4—7.0 (1H, m, $C\underline{H}=CHCO$), 7.28 (5H, s, Ar-H). MS *m/e* (%): 345 (15, M^+), 210 (83), 91 (100). High-resolution MS Calcd for $C_{19}H_{23}NO_5$: 345.1574. Found: 345.1570.

b) From **18**: The Jones reagent[12] (8 N; 0.8 ml) was added dropwise to a stirred solution of **18** (705 mg) in purified acetone (6 ml) under ice cooling over a period of 1 h. After decomposition of the excess reagent with MeOH, the mixture was diluted with water (10 ml) and extracted with $CHCl_3$ (20 ml × 3). The extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 489 mg (70%) of **9**, which was proved to be identical with the sample obtained in a) by means of TLC, IR, and ^{1}H-NMR comparisons.

Benzyl *endo*- and *exo*-7-Ethoxycarbonylmethyl-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (19 and 20)——a) A mixture of **9** (450 mg), anhydrous K_2CO_3 (0.40 g), and abs. EtOH (40 ml) was refluxed with stirring in a stream of N_2 for 30 min. The pH of the mixture was adjusted to 6 with 10% HCl and the ethanol was evaporated off. The residue was extracted with $CHCl_3$ (70 ml) and the extract was washed with brine. The dried extract was concentrated to leave an oily residue, which was chromatographed on alumina in $CHCl_3$–hexane (1 : 1). The first fraction afforded 331 mg (73%) of **19** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (COO), 1685 (NCOO). ^{1}H-NMR δ: 1.21 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 3.44 (2H, br d, $J=3$ Hz, C_3-H), 4.06 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 4.21 (1H, br d, $J=3$ Hz, C_1-H), 5.07 (2H, s, CH_2Ar), 7.25 (5H, s, Ar-H). MS *m/e* (%): 345 (3, M^+), 317 (87), 158 (100). High-resolution MS Calcd for $C_{19}H_{23}NO_5$: 345.1574. Found: 345.1559. The second fraction afforded 69 mg (15%) of **20** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (COO), 1685 (NCOO). ^{1}H-NMR δ: 1.20 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 3.38 (2H, br s, C_3-H), 4.03 (2H, br q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 5.07 (2H, s, CH_2Ar), 7.24 (5H, s, Ar-H). MS *m/e* (%): 345 (31, M^+), 317 (79), 158 (100). High-resolution MS Calcd for $C_{19}H_{23}NO_5$: 345.1574. Found: 345.1534.

b) A mixture of **9** (93 mg), NaH (50% in oil; 7.5 mg), and abs. dioxane (10 ml) was refluxed with stirring for 4.5 h. After neutralization with 10% HCl, the mixture was concentrated and the residue was taken in $CHCl_3$ (30 ml). Work-up as usual gave 47 mg (51%) of **19** and 24 mg (26%) of **20**.

Benzyl *endo*-7-Ethoxycarbonylmethyl-6,6-dimethoxy-2-azabicyclo[2.2.2]octane-2-carboxylate (21)——A mixture of **19** (327 mg), methyl orthoformate (0.5 ml), *p*-TsOH (trace), and abs. MeOH (20 ml) was refluxed with stirring for 1 h. The solvent was evaporated off and the residue was taken up in $CHCl_3$ (40 ml). The $CHCl_3$ solution was washed with sat. $NaHCO_3$ and brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 374 mg (100%) of **21** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (COO), 1685 (NCOO). ^{1}H-NMR δ (35 °C): 3.05 (3H, s, OCH_3), 3.17 (3H, s, OCH_3), 5.15 (2H, s, CH_2Ar), 7.31 (5H, s, Ar-H). MS *m/e* (%): 391 (24, M^+), 91 (100).

Benzyl *endo*-7-(2-Hydroxyethyl)-6,6-dimethoxy-2-azabicyclo[2.2.2]octane-2-carboxylate (22)——A solution of **21** (374 mg) in abs. ether (8 ml) was added to a suspension of $LiAlH_4$ (120 mg) in abs. ether (6 ml), and the mixture was stirred under ice cooling for 30 min. After decomposition of the excess $LiAlH_4$ with AcOEt, sat. Rochelle salt solution was added to the mixture and inorganic substances were filtered off. The filtrate was dried and concentrated to leave an oily residue, which was chromatographed on alumina in $CHCl_3$ to afford 304 mg (92%) of **22** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (OH), 1680 (NCOO). ^{1}H-NMR δ: 2.20 (1H, s, OH), 3.00 (3H, s, OCH_3), 3.13 (3H, s, OCH_3), 3.23 (2H, br s, C_3-H), 3.58 (2H, t, $J=6$ Hz, $C\underline{H}_2OH$), 4.02—4.17 (1H, m, C_1-H), 5.02 (2H, s, CH_2Ar), 7.20 (5H, s, Ar-H). MS *m/e* (%): 349 (5.5, M^+), 290 (48), 91 (100).

Benzyl 3-Hydroxy-4-oxa-9-azatricyclo[5.3.1.0^{3,8}]undecane-9-carboxylate (23)——A solution of **22** (92 mg) in purified acetone (2 ml) containing 1% HCl (1 ml) was refluxed for 30 min, then cooled. The acetone was evaporated off and the residue was extracted with $CHCl_3$ (10 ml × 3). The extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (20 : 1) to afford 66 mg (83%) of **23** as a colorless oil. The product solidified on standing overnight, and recrystallization from hexane provided a white powder, mp 85—87 °C. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1675 (NCOO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370 (OH), 1735 (CO), 1685 (NCOO). ^{1}H-NMR δ: 5.05 (2H, s, CH_2Ar), 7.22 (5H, s, Ar-H). MS *m/e* (%): 303 (1.4, M^+), 275 (18), 91 (100). *Anal.* Calcd for $C_{17}H_{22}NO_4$: C, 66.31; H, 6.98; N, 4.62. Found: C, 66.72; H, 6.98; N, 4.47.

Benzyl *endo*-7-(2-Methanesulfonyloxyethyl)-6,6-dimethoxy-2-azabicyclo[2.2.2]octane-2-carboxylate (24)——Methanesulfonyl chloride (0.3 ml) and Et_3N (0.3 ml) were added to a solution of **22** (388 mg) in dry C_6H_6 (10 ml), and the mixture was allowed to stand at room temperature for 3 h, then diluted with C_6H_6 (30 ml) and washed with 2% HCl and brine. Concentration of the dried organic layer left an oily residue, which was chromatographed on alumina in $CHCl_3$–C_6H_6 (1 : 1) to afford 458 mg (96%) of **24** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (NCOO), 1350, 1170 (SO_2). ^{1}H-NMR δ: 2.82, 2.93, 2.98, 3.09, 3.13 (total 9H, each s, $OCH_3 \times 2$, SCH_3), 3.23 (2H, br s, C_3-H), 3.93—4.34 (3H, m, C_1-H, CH_2OMs), 5.07 (2H, s, CH_2Ar), 7.22 (5H, s, Ar-H). MS *m/e* (%): 427 (4, M^+), 368 (17), 110 (47), 91 (100).

Benzyl *endo*-7-(2-Methanesulfonyloxyethyl)-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (25)——A solution of **24** (225 mg) in purified acetone (4 ml) containing 1% HCl (2 ml) was refluxed for 30 min. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 185 mg (92%) of **25** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1732 (CO), 1685 (NCOO). ^{1}H-NMR δ: 2.8—3.0 (3H, m, SCH_3), 5.12 (2H, t, $J=6$ Hz, CH_2OMs), 5.05 (2H, s, CH_2Ar), 7.22 (5H, s, Ar-H).

Benzyl 2-Oxo-4-azatwistane-4-carboxylate (26)——A solution of **25** (183 mg) in dry DMF (7 ml) was added all at once to a suspension of NaH (50% in oil; 14 mg) in dry DMF (2 ml), and the mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized with AcOH and the organic solvent was evaporated off. The residue was taken up in ether (40 ml) and the ethereal solution was washed with brine. Concentration of the dried ethereal layer left an oily residue, which was chromatographed on alumina in $CHCl_3$–C_6H_6 (1 : 1) to afford 54 mg (39%) of **26** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745 (CO), 1685 (NCOO). ^{1}H-NMR δ: 4.18 (1H, m, C_3-H), 5.04 (2H, s, CH_2Ar), 7.20 (5H, s, Ar-H). MS *m/e* (%): 285 (1.4, M^+), 257 (96), 91 (100).

Benzyl *endo*-7-Ethyl-6,6-dimethoxy-2-azabicyclo[2.2.2]octane-2-carboxylate (27)——A mixture of **24** (458 mg), NaI (804 mg), zinc dust (697 mg), and abs. DME (10 ml) was refluxed with stirring for 3 h. The inorganic substances were filtered off and the filtrate was concentrated. The residue was taken up in $CHCl_3$ (40 ml) and the organic solution was washed with water. Concentration of the dried organic layer left an oily residue, which was chromatographed on alumina in $CHCl_3$–C_6H_6 to afford 303 mg (85%) of **27** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (NCOO). ^{1}H-NMR δ: 0.87 (3H, t, $J=6$ Hz, C_7-$CH_2C\underline{H}_3$), 3.07, 3.13, 3.17, 3.20 (total 6H, each s, $OCH_3 \times 2$), 3.27 (2H, s, C_3-H), 4.00, 4.12 (total 1H, each d, $J=2$ Hz, C_1-H), 5.12 (2H, s, CH_2Ar), 7.27 (5H, s, Ar-H). MS *m/e* (%): 333 (42, M^+), 274 (100), 91 (96).

Benzyl *endo*-7-Ethyl-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (28)——A solution of **27** (281 mg) in purified acetone (6 ml) containing 1% HCl (3 ml) was refluxed for 30 min. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$–EtOH (100 : 1) to afford 246 mg (100%) of **28** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (CO), 1685 (NCOO). ^{1}H-NMR δ (DMSO-d_6; at 100 °C): 0.85 (3H, t, $J=6$ Hz, C_7-$CH_2C\underline{H}_3$), 4.04 (1H, d, $J=4$ Hz, C_1-H), 5.10 (2H, s, CH_2Ar), 7.33 (5H, s, Ar-H). High-resolution MS Calcd for $C_{17}H_{21}NO_3$: 287.1520. Found: 287.1489.

***endo*-7-Ethyl-2-(3-indolylacetyl)-2-azabicyclo[2.2.2]octan-6-one (30)**——A solution of **28** (65 mg) in abs. MeOH (10 ml) was hydrogenated over 5% Pd–C (80 mg) under atmospheric pressure of H_2 at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated to afford the crude amine (**29**). A solution of 3-indolylacetyl chloride (50 mg) in CH_2Cl_2 (5 ml) and a solution of anhyd. K_2CO_3 (140 mg) in water (5 ml) were added to a stirred solution of the product (**29**) in CH_2Cl_2 (20 ml) under ice cooling over a period of 2—3 min, and the mixture was further stirred at room temperature for 5 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 ml × 2). The combined organic layer was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on alumina in $CHCl_3$ to afford 65 mg (93%) of **30** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 1725 (CO), 1625 (NCOO). ^{1}H-NMR δ: 0.58 (3H, t, $J=6$ Hz, C_7-$CH_2C\underline{H}_3$), 3.45 (2H, br s, C_3-H), 3.70, 3.77 (total 2H, each s, CH_2Ar), 3.98, 4.73 (total 1H, each d, $J=2$ Hz, C_1-H), 6.8—7.7 (5H, m, Ar-H), 8.70 (1H, br s, NH). MS *m/e* (%): 310 (100, M^+), 282 (18), 152 (56).

***endo*-7-Ethyl-2-(3-indolylacetyl)-6,6-dimethoxy-2-azabicyclo[2.2.2]octane (31)**——A mixture of **30** (65 mg), methyl orthoformate (0.4 ml), *p*-TsOH (trace), and abs. MeOH (10 ml) was refluxed with stirring for 2 h. Work-up as usual gave an oily residue, which was chromatographed on alumina in $CHCl_3$ to afford 61 mg (82%) of

31 as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3470 (NH), 1625 (NCO). ^{1}H-NMR δ: 0.50, 0.85 (total 3H, each t, J=6 Hz, C$_7$-CH$_2$C$\underline{\mathrm{H}}_3$), 3.06, 3.12, 3.13 (total 6H, each s, OCH$_3$ × 2), 4.59 (1H, d, J=2 Hz, C$_1$-H), 6.8—7.6 (5H, m, Ar-H), 8.57 (1H, br s, NH). MS m/e (%): 356 (22, M$^+$), 184 (73), 120 (100).

(±)-18-Tosyloxy-7-oxo-epiibogamine (32)——A solution of **31** (61 mg) in dry C_6H_6 (5 ml) was added all at once to a stirred, boiling solution of anhyd. *p*-TsOH (40 mg) in dry C_6H_6 (15 ml), and the mixture was refluxed with stirring for 5 min while C_6H_6 was very slowly distilled off in order to remove the formed methanol. The cooled reaction mixture was diluted with C_6H_6 (10 ml) and the resulting mixture was washed with sat. $NaHCO_3$ and brine. Concentration of the dried organic layer left an oily residue, which was chromatographed on alumina in $CHCl_3$ to afford 63 mg (79%) of **32** as colorless crystals. Recrystallization from C_6H_6–hexane provided colorless needles, mp 176—178 °C (lit.[5h] mp 175—178 °C). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3450 (NH), 1630 (NCO), 1360, 1175 (SO$_2$). ^{1}H-NMR δ: 0.77 (3H, t, J=6.5 Hz, CH$_2$C$\underline{\mathrm{H}}_3$), 2.39 (3H, s, Ar-CH$_3$), 3.75 (2H, s, C$_8$-H), 4.79 (1H, d, J=3 Hz, C$_4$-H), 7.0—7.6 (6H, m, Ar-H), 7.54 (2H, d, J=8.5 Hz, Ar-H), 8.04 (1H, br s, NH). MS m/e (%): 292 (67, M$^+$ − TsOH), 223 (100). *Anal.* Calcd for $C_{26}H_{28}N_2O_4S$: C, 67.22; H, 6.08; N, 6.03. Found: C, 67.42; H, 6.43; N, 6.05.

(±)-Epiibogamine (2)——Lithium aluminum hydride (147 mg) was added portionwise to a stirred solution of anhyd. $AlCl_3$ (516 mg) in abs. THF (8 ml) at room temperature over a period of 1 min. Stirring was continued for several min, then a solution of **32** (50 mg) in abs. THF (2 ml) was added all at once and the resulting mixture was further stirred at room temperature for 2.5 h. The excess reducing agent was decomposed with AcOEt and the mixture was diluted with THF (30 ml). Sat. Rochelle salt solution and then conc. NH_3 aq. solution were added to the mixture. The whole was stirred for 3 h at room temperature, then the inorganic substances were filtered off and the filtrate was concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (10 : 1) to afford 26 mg (86%) of **2** as colorless prisms, mp 197—199 °C (from EtOH) (lit.[5h] mp 196.5—197.5 °C). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3450 (NH). ^{1}H-NMR δ: 0.93 (3H, t, J=7 Hz, CH$_2$C$\underline{\mathrm{H}}_3$), 6.9—7.5 (4H, m, Ar-H), 7.95 (1H, br s, NH). MS m/e (%): 280 (20, M$^+$), 149 (87), 43 (100). High-resolution MS Calcd for $C_{19}H_{24}N_2$: 280.1938. Found: 280.1929. The synthetic product was proved to be identical with natural epiibogamine by means of TLC, IR, and ^{1}H-NMR comparisons.

Benzyl *exo*-7-Ethoxycarbonylmethyl-6,6-dimethoxy-2-azabicyclo[2.2.2]octane-2-carboxylate (33)——A mixture of **20** (63 mg), methyl orthoformate (0.5 ml), *p*-TsOH (trace), and abs. MeOH (10 ml) was refluxed with stirring for 1 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 67 mg (94%) of **33** as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720 (COO), 1685 (NCOO). ^{1}H-NMR δ: 1.15, 1.22 (total 3H, each t, J=7 Hz, OCH$_2$C$\underline{\mathrm{H}}_3$), 3.03, 3.12, 3.14, 3.17 (total 6H, each s, OCH$_3$ × 2), 5.06, 5.08 (total 2H, each s, CH$_2$Ar), 7.17, 7.19 (total 5H, each s, Ar-H). MS m/e (%): 391 (5, M$^+$), 332 (34), 301 (100), 91 (98). High-resolution MS Calcd for $C_{21}H_{29}NO_6$: 391.1992. Found: 391.1979.

Benzyl *exo*-7-(2-Hydroxyethyl)-6,6-dimethoxy-2-azabicyclo[2.2.2]octane-2-carboxylate (34)——A solution of **33** (340 mg) in abs. ether (8 ml) was added to a stirred suspension of $LiAlH_4$ (110 mg) in abs. ether (6 ml) under ice cooling over a period of 1 min, and the mixture was further stirred under cooling for 15 min. Work-up as usual gave an oily residue, which was chromatographed on alumina in $CHCl_3$ to afford 279 mg (92%) of **34** as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3420 (OH), 1670 (NCOO). ^{1}H-NMR δ: 3.00, 3.10, 3.13 (total 6H, each s, OCH$_3$ × 2), 3.88, 4.03 (total 1H, each br s, C$_1$-H), 5.03 (2H, s, CH$_2$Ar), 7.18 (5H, s, Ar-H). MS m/e (%): 349 (15, M$^+$), 290 (24), 274 (27), 259 (90), 91 (100).

Benzyl *exo*-7-(2-Methanesulfonyloxyethyl)-6,6-dimethoxy-2-azabicyclo[2.2.2]octane-2-carboxylate (35)——Methanesulfonyl chloride (0.3 ml) and Et_3N (0.3 ml) were added to a solution of **34** (279 mg) in dry C_6H_6 (20 ml), and the mixture was allowed to stand at room temperature for 2 h. Work-up as usual gave an oily residue, which was chromatographed on alumina in $CHCl_3$–hexane (1 : 1) to afford 311 mg (91%) of **35** as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1680 (NCOO), 1350, 1165 (SO$_2$). ^{1}H-NMR δ: 2.80, 2.90, 3.00, 3.10, 3.13 (total 9H, each s, OCH$_3$ × 2, SCH$_3$), 3.90—4.33 (3H, m, C$_1$-H, CH$_2$OMs), 5.04 (2H, s, CH$_2$Ar), 7.18 (5H, s, Ar-H). MS m/e (%): 427 (19, M$^+$), 337 (100), 91 (88).

Benzyl *exo*-7-Ethyl-6,6-dimethoxy-2-azabicyclo[2.2.2]octane-2-carboxylate (36)——A mixture of **35** (310 mg), NaI (545 mg), zinc dust (472 mg), and abs. DME (10 ml) was refluxed with stirring for 3 h. Work-up as usual gave an oily residue, which was chromatographed on alumina in $CHCl_3$ to afford 205 mg (85%) of **36** as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1675 (NCOO). ^{1}H-NMR δ: 0.93 (3H, t, J=5.5 Hz, C$_7$-CH$_2$C$\underline{\mathrm{H}}_3$), 3.02, 3.12, 3.15 (total 6H, each s, OCH$_3$ × 2), 3.91, 4.03 (total 1H, each s, C$_1$-H), 5.07 (2H, s, CH$_2$Ar), 7.20 (5H, s, Ar-H). MS m/e (%): 333 (45, M$^+$), 274 (54), 243 (100), 91 (79).

Benzyl *exo*-7-Ethyl-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (37)——A solution of **36** (194 mg) in purified acetone (6 ml) containing 1% HCl (3 ml) was refluxed for 30 min. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (100 : 1) to afford 168 mg (100%) of **37** as a colorless oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1730 (CO), 1680 (NCOO). ^{1}H-NMR δ (DMSO-d_6; at 110 °C): 0.85 (3H, t, J=6.5 Hz, C$_7$-CH$_2$C$\underline{\mathrm{H}}_3$), 3.37 (2H, br s, C$_3$-H), 4.06 (1H, d, J=1.2 Hz, C$_1$-H), 5.10 (2H, s, CH$_2$Ar), 7.32 (5H, s, Ar-H). High-resolution MS Calcd for $C_{17}H_{21}NO_3$: 287.1519. Found: 287.1509.

***exo*-7-Ethyl-2-(3-indolylacetyl)-2-azabicyclo[2.2.2]octan-6-one (39)**——A solution of **37** (198 mg) in abs. MeOH (15 ml) was hydrogenated over 5% Pd–C (100 mg) under atmospheric pressure of H_2 at room temperature for 20 min. The catalyst was filtered off and the filtrate was concentrated to give crude **38**. A solution of 3-

indolylacetyl chloride (200 mg) in CH_2Cl_2 (5 ml) and a solution of anhyd. K_2CO_3 (360 mg) in water (5 ml) were added to a stirred solution of the product in CH_2Cl_2 (20 ml) under ice cooling over a period of 2—3 min, and the mixture was further stirred under cooling for 5 min. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (10 : 1) to afford 174 mg (81%) of **39** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 1730 (CO), 1625 (NCO). ^{1}H-NMR δ (DMSO-d_6; at 120 °C): 0.81 (3H, t, $J=7$ Hz, C_7-$CH_2C\underline{H}_3$), 3.51 (2H, br s, C_3-H), 3.71 (2H, s, CH_2Ar), 4.40 (1H, br s, C_1-H), 6.82—7.56 (5H, m, Ar-H), 8.14 (1H, s, NH). MS m/e (%): 310 (44, M^+), 130 (100). High-resolution MS Calcd for $C_{19}H_{22}N_2O_2$: 310.1679. Found: 310.1664.

***exo*-7-Ethyl-2-(3-indolylacetyl)-6,6-dimethoxy-2-azabicyclo[2.2.2]octane (40)**——A mixture of **39** (164 mg), methyl orthoformate (1.0 ml), p-TsOH (trace), and abs. MeOH (15 ml) was refluxed with stirring for 30 min. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (20 : 1) to afford 187 mg (99%) of **40** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (NH), 1625 (NCO). ^{1}H-NMR δ: 3.05, 3.08, 3.13 (total 6H, each s, $OCH_3 \times 2$), 3.28 (2H, br s, C_3-H), 3.65 (2H, s, CH_2Ar), 3.77, 4.55 (total 1H, each s, C_1-H), 6.73—7.50 (5H, m, Ar-H), 8.67 (1H, br s, NH). MS m/e (%): 356 (84, M^+), 184 (100), 149 (85), 130 (81).

(±)-18-Tosyloxy-7-oxo-ibogamine (41)——A solution of **40** (47 mg) in dry C_6H_6 (5 ml) was added all at once to a stirred boiling solution of anhyd. p-TsOH (47 mg) in dry C_6H_6 (10 ml), and the mixture was refluxed with stirring for 10 min while C_6H_6 was very slowly distilled off in order to remove the formed methanol. Work-up as usual gave an oily residue, which was chromatographed on alumina in $CHCl_3$–hexane (2 : 1) to afford 44 mg (72%) of **41** as colorless cubes, mp 140—145 °C (from hexane) (lit.[5b] amorphous). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH), 1630 (NCO), 1360, 1170 (SO_2). ^{1}H-NMR δ: 1.00 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.10 (3H, s, Ar-CH_3), 3.26, 3.56 (2H, AB-q, $J=20$ Hz, C_8-H), 4.13 (1H, s, C_4-H), 6.63 (2H, d, $J=8$ Hz, Ar-H), 6.9—7.3 (6H, m, Ar-H), 8.38 (1H, br s, NH). MS m/e (%): 464 (0.1, M^+), 292 (70), 223 (100).

(±)-Ibogamine (1)——Lithium aluminum hydride (133 mg) was added portionwise to a stirred solution of anhyd. $AlCl_3$ (465 mg) in abs. THF (8 ml) at room temperature over a period of 1 min. The mixture was stirred for several min, then a solution of **41** (45 mg) in abs. THF (2 ml) was added all at once and the resulting mixture was further stirred at room temperature for 2.5 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (20 : 1) to afford 20 mg (74%) of **1** as a colorless oil, which was triturated with hexane to provide a white powder, mp 130—132 °C (lit.[5b] 127—128 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH). ^{1}H-NMR δ: 0.90 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 7.0—7.5 (4H, m, Ar-H), 7.60 (1H, br s, NH). MS m/e (%): 280 (100, M^+), 136 (98). High-resolution MS Calcd for $C_{19}H_{24}N_2$: 280.1937. Found: 280.1935. The synthetic product was proved to be identical with natural ibogamine by means of TLC, IR, ^{1}H-NMR comparisons.

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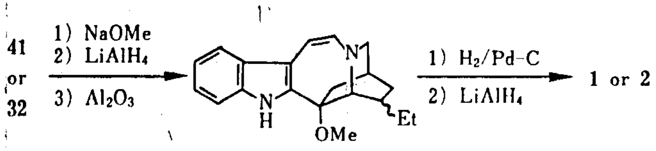

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